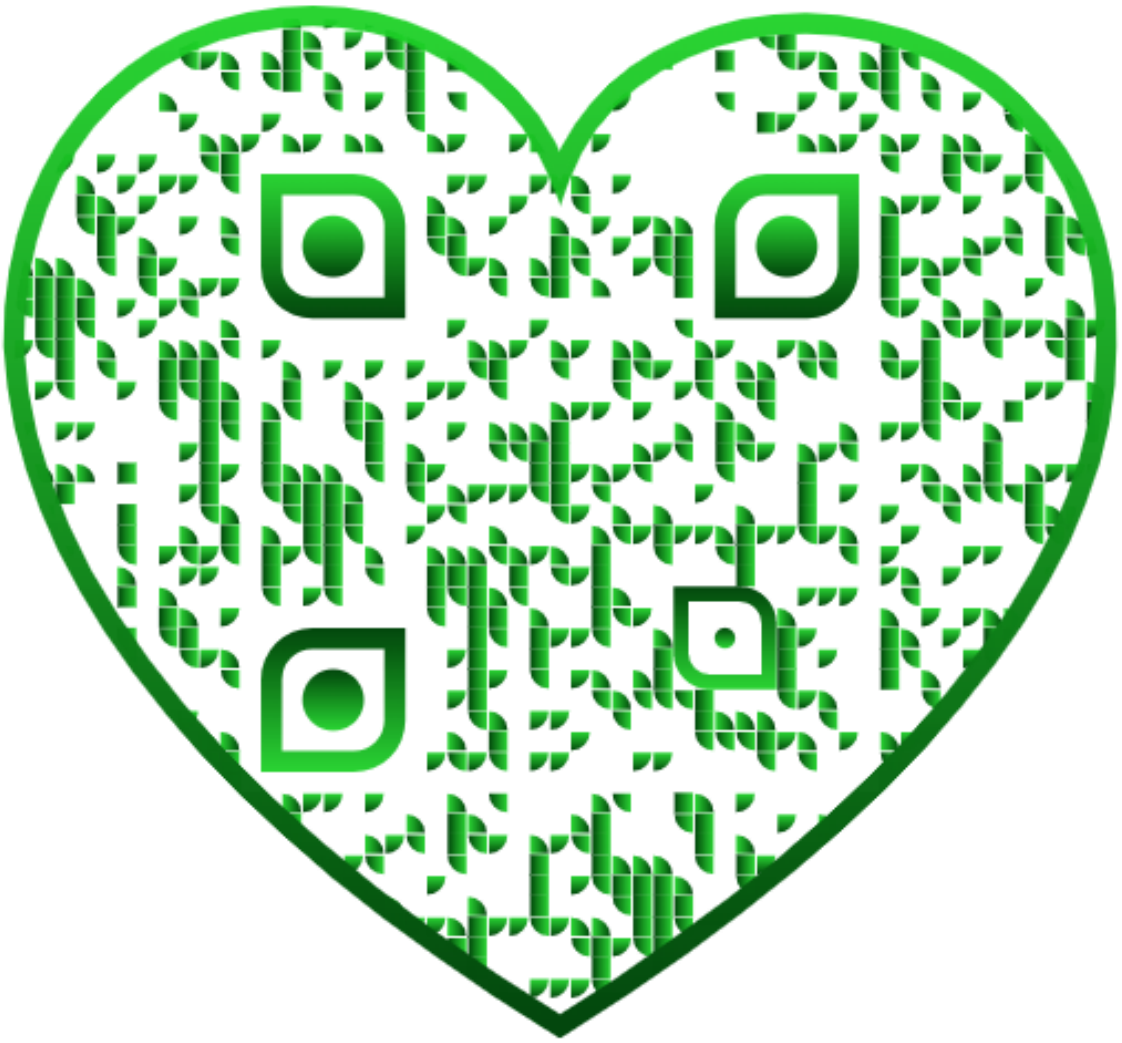
2.3 Non-linear Pharmacokinetics



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- After administration of several different doses until steady state is established, if a plot of steady state concentration (C_{ss}) vs dose yields a straight line, the drug is said to follow linear PK.

- When C_{ss} change in a disproportionate fashion after the dose is altered, a plot of C_{ss} Vs dose is not a straight line and the drug is said to follow non-linear PK.

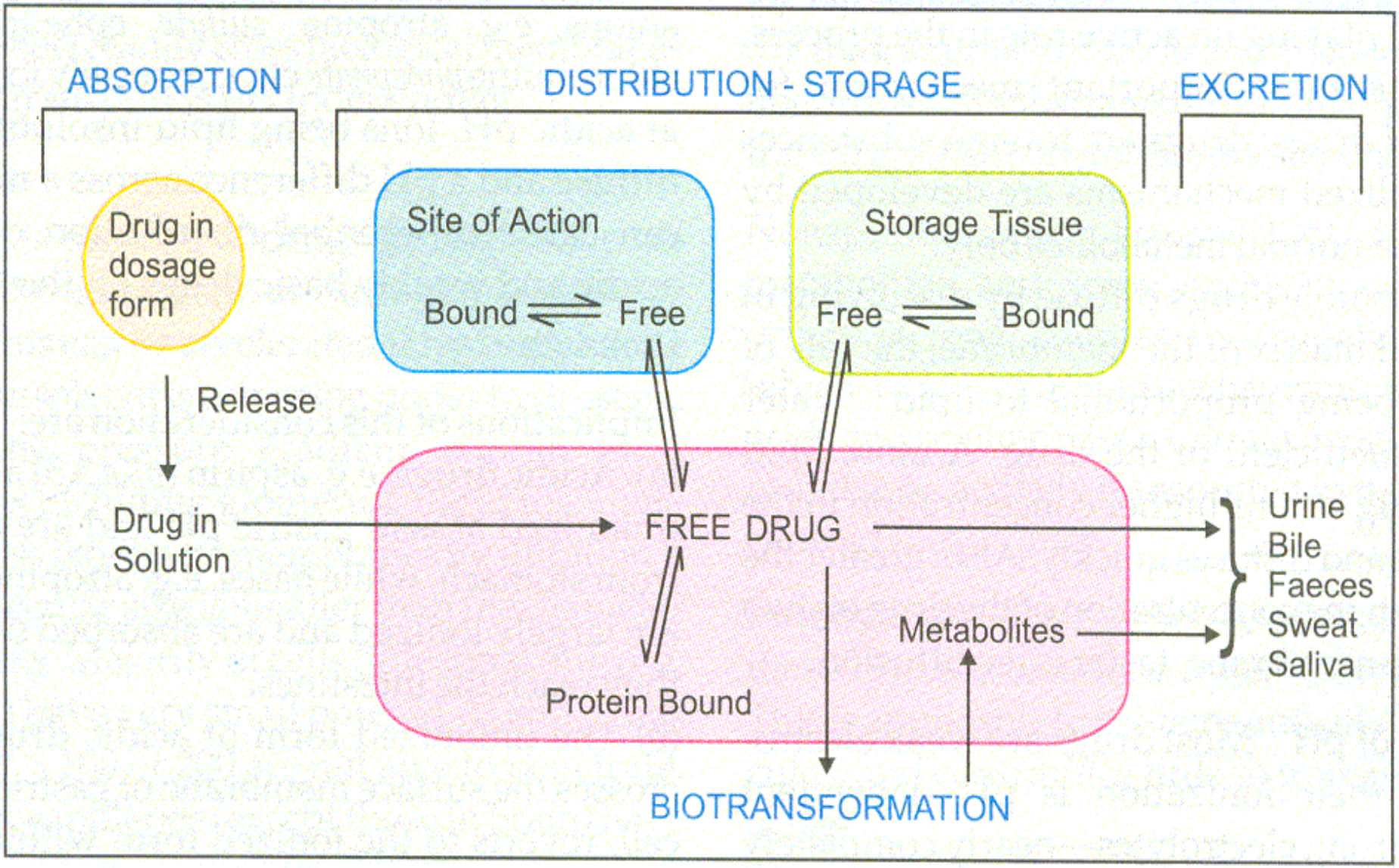
■ ■ ■

- The time of administration of a drug may also influence the pharmacokinetic parameters of the drug, which are termed as time dependent pharmacokinetics.
  - Time dependency involves an actual physiological or biochemical change in the organ(s) of the body associated with the drug disposition parameters in question.
  - For example, in time dependence of the auto- or hetero-induction type, the increase in drug intrinsic clearance results from an increase in amount of enzyme (in protein synthesis).

2.4 Drug ADME Processes

■ ■ ■

- ADME describes the disposition of a drug within a body.
- These processes influence the drug levels and kinetics of drug exposure to the tissues and hence influence the performance and pharmacological activity of the drug.


ABSORPTION
DISTRIBUTION - STORAGE
EXCRETION
Drug in dosage form
Release
Drug in Solution
Site of Action
Bound ⇌ Free
Storage Tissue
Free ⇌ Bound
FREE DRUG
Protein Bound
BIOTRANSFORMATION
Metabolites
Urine
Bile
Faeces
Sweat
Saliva

Drug Absorption

- Absorption is the transfer of **unchanged** drug from its site of administration to the blood stream.
- Most drugs are absorbed by passive diffusion across a biologic barrier
  - Lipid diffusion
  - Aqueous diffusion
- A few drugs are absorbed by active transport or by facilitated diffusion.

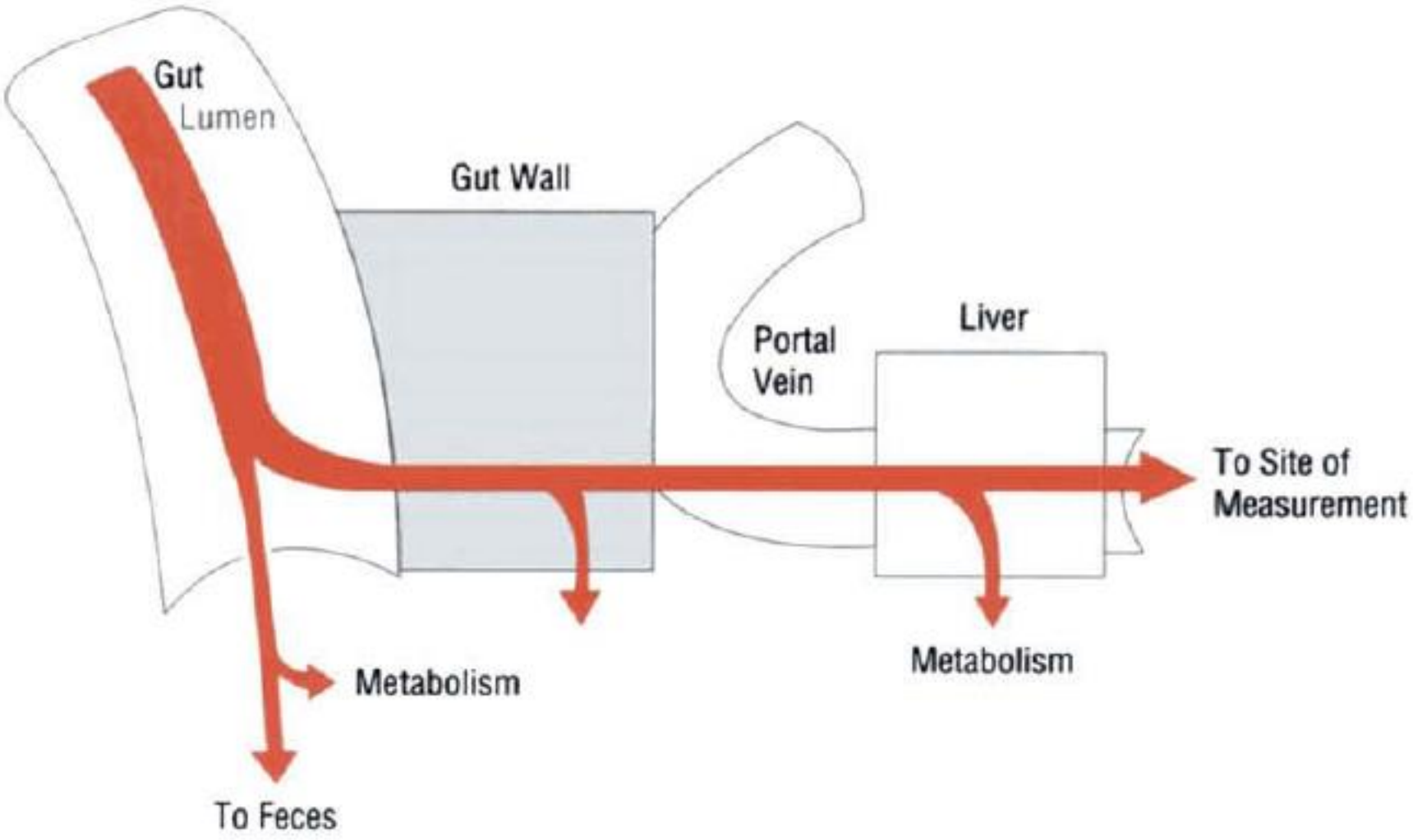


Fig. Steps involved in the absorption of a drug given orally.

■ ■ ■

- Many PK studies are concerned principally with the bioavailability of the drug.

- A drug that is absorbed slowly may not achieve sufficiently high concentrations at the site of action to elicit a desired effect or intensity of effect, even if the entire dose is absorbed.

- The extent of absorption is usually the more important factor for drugs that are administered repetitively for the treatment of subchronic or chronic conditions

■ ■ ■

- The average drug concentration in plasma at steady state during repetitive administration is directly proportional to the amount absorbed from each dose but is independent of the rate of absorption.

- The rate of absorption does, however, influence the time course of drug concentration in plasma during a dosing interval at steady state.

- For drugs administered extravascularly and intended to act systemically, absorption is a prerequisite for pharmacological effects.

First-order absorption

- First-order absorption means the absorption rate is proportional to the amount of drug at the absorption site.
    - Typically this means that the absorption rate is higher immediately after the dose is given and the rate then decreases as drug is absorbed.
- The fractional rate of decline is constant for a first-order process.
- The oral absorption of drugs often approximates first order kinetics, especially when given in solution.

■ ■ ■

Zero-order absorption process

- Sometimes, a drug is absorbed at essentially a constant rate.
- In zero-order absorption process, the fractional rate increases with time, because the rate is constant but the amount remaining decreases.
- This can be achieved by a constant rate intra-venous infusion.
    - It can also be approximated by some kinds of oral dosing.

Drug Distribution

- **Distribution ~**
  - Reversible transfer of a drug to and from the site of measurement (blood or plasma).
  - It is the passage of drug from the circulation to the tissue and site of its action.
  - Volume of plasma in which the total amount of drug in the body would be required to be dissolved in order to reflect the drug concentration attained in plasma.

■ ■ ■

- The extent of distribution of drug depends on its:
  - Lipid solubility
  - Ionization at physiological pH (dependent on pKa)
  - Extent of binding to plasma and tissue proteins
  - Differences in regional blood flow

Volume of distribution

- The volume that would accommodate all the drugs in the body.
- A hypothetical volume that relates drug serum concentrations to the amount of drug in the body.
- It has no direct physiological meaning; it is not a 'real' volume and is usually referred to as the apparent volume of distribution.

■ ■ ■

- It is important to realize that the C_p in plasma is not necessarily the same in the liver, kidney or other tissues.

- Thus, amount of drug in plasma does not equal to amount of drug (X) in the kidney or amount of drug (X) in the liver or amount of drug (X) in tissues.

- However, changes in the C_p are proportional to changes in the amount of drug (X) in the tissues.

■ ■ ■

- Since C_p(plasma) ∝ X(tissues)
  - Then X (tissues) = V_d . C_p (plasma)

V_d being the proportionality constant

- V_d thus relates the total amount of drug in the body at any time to the corresponding plasma concentration.

$$V_d = \frac{X}{C_p}$$

■ ■ ■

- The volume of distribution is an important parameter for determining proper drug dosing.
- Generally, dosing is proportional to the volume of distribution.
- V_d is useful in relating amount in body to plasma concentration.

■ ■ ■

- Knowing plasma volume (V_p), and V_d the fraction of drug in the body **in** and **outside plasma** can be estimated.

$$Fraction\ of\ drug\ in\ plasma = \frac{V_p}{V_d}$$

$$Fraction\ of\ drug\ outside\ plasma = \frac{V_d - V_p}{V_d}$$

Factors affecting drug distribution

- These factors may affect the rate and/or extent of distribution
  - **Rate of distribution:** Membrane/tissue permeability, and Blood perfusion
  - **Extent of distribution:** Physicochemical properties of the drug, and protein binding.

Drug distribution and tissue permeability

- The rate of blood flow to tissue capillaries varies widely as a result of unequal distribution of cardiac output to various organs.

- The drug distribution to a particular organ or tissue depends on the **size of the tissue** and **tissue perfusion rate**.

- **Protein binding** and **ionization** will affect transfer rate across membranes, with only one species (unbound, un-ionized form) capable of traversing membranes.

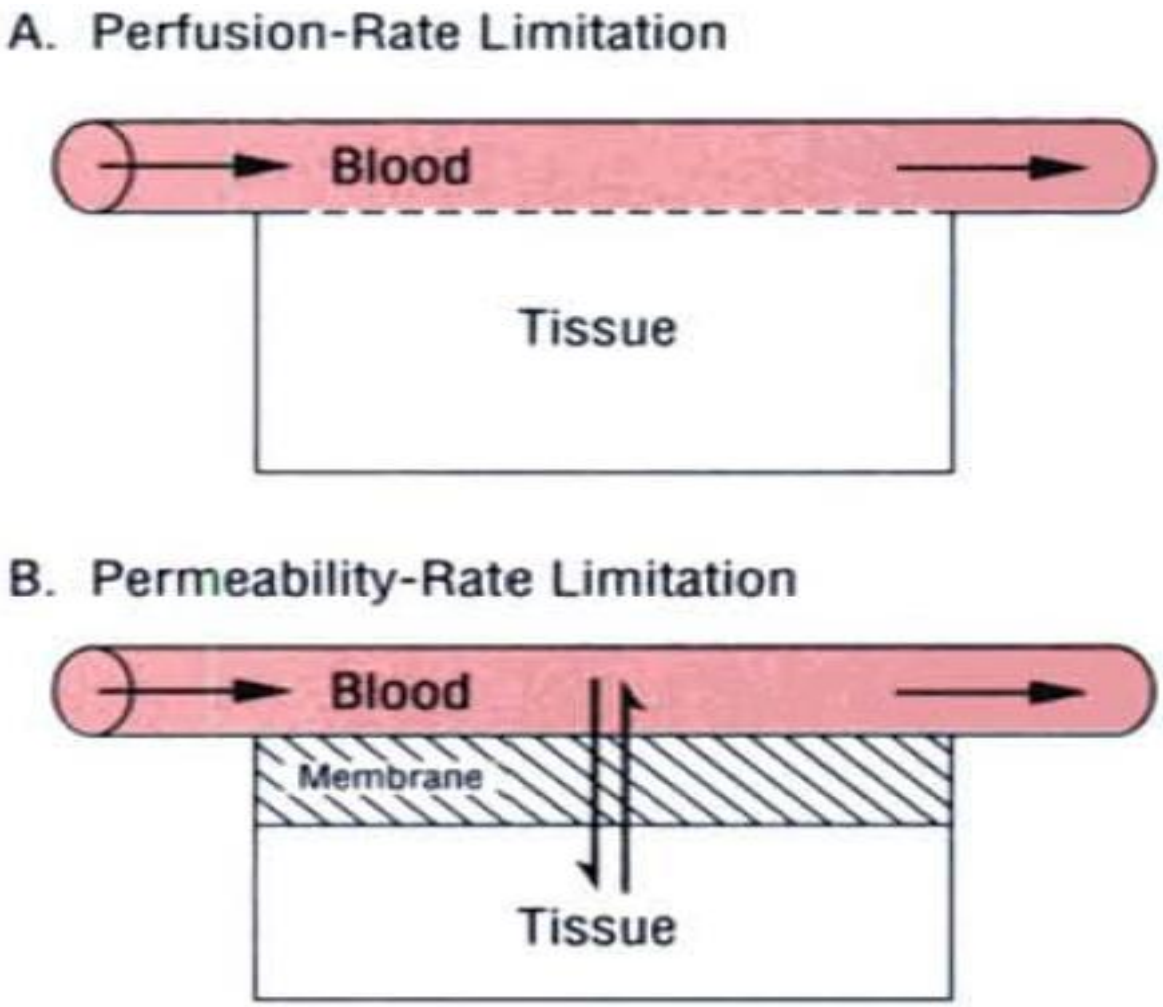


Fig. The limiting steps controlling rate of movement of drugs across a membrane, from blood to tissues or vise versa, varies.

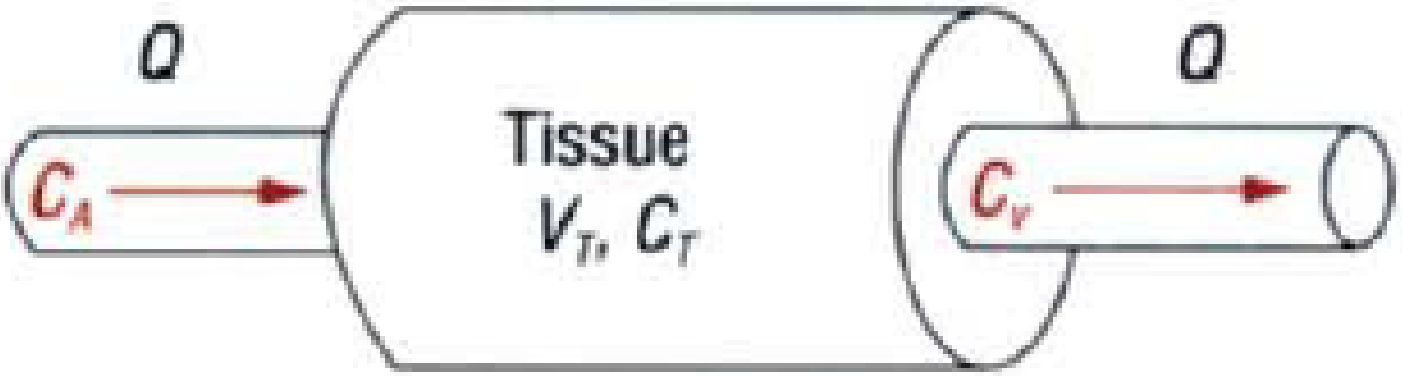


Fig. Blood perfussing a tissue in which distribution is perfusion rate limited and no elimination occurs.

■ ■ ■

- Drug is presented to a tissue at an arterial blood concentration of C_A and at a rate equal to the product of blood flow (Q) and C_A

$$\text{Rate of presentation} = Q \times C_A$$

- The drug leaves the tissue at a venous concentration C_V and at a rate equal to $Q.C_V$

$$\text{Rate of leaving} = Q \times C_V$$

$$\textbf{Net Rate of uptake} = \mathbf{Q\,(C_A - C_V)}$$

■ ■ ■

- The tissue concentration, C_T, increases when rate of presentation exceeds rate of leaving in the venous blood, and the converse.

- The amount in the tissue at any time t is:

$$Q_T = V_T \times K_p \times C_V$$

V_T is the tissue volume and K_p is the equilibrium distribution ratio (C_T/C_V).

■ ■ ■

- Furthermore, the fractional rate of exit, k_T, is given by:

$$k_T = \frac{Rate\ of\ exit}{Amount\ in\ tissue} = \frac{Q.C_V}{V_T.k_p.C_V}$$

Or

$$k_T = \frac{{}^{Q}/_{V_T}}{k_p}$$

Where ${}^{Q}/_{V_T}$ is perfusion rate of the tissue

Drug distribution and Protein binding

- Drugs are transported in the circulating blood in two forms: free form and bound form.
- Free form of drugs is usually dissolved in plasma and is pharmacologically active, diffusible, and available for metabolism and excretion.
- Drugs may bind to plasma or tissue proteins.

■■■

- Plasma-protein binding:
  - Affects distribution
  - PPB drug is pharmacologically inactive
  - Non-diffusible
  - Not available for metabolism or excretion
- The plasma protein binding of drugs is usually reversible

■■■

- The binding of individual drugs ranges from very little (e.g., Theophylline) to very high (e.g. warfarin).
- In circulating blood, there is a constant ratio between the bound and free fractions of the drug.
- When the concentration of the free drug falls, the **free-to-bound** ratio is maintained by dissociation of the bound form of the drug.

■ ■ ■

- The fraction of drug in plasma unbound (f_u) is very important in therapeutics.

$$f_u = \frac{C_u}{C}$$

Where, C_u-is concentration of the unbound drug, and C-is the concentration in plasma.

- The degree of binding can also be expressed as the bound-to-total concentration ratio. This ratio has values between 0 an 1.0
    - Drugs having values greater than 0.9 are said to be highly bound.

■ ■ ■

- Binding is a function of affinity of the proteins to the drug.
  - This is characterized by association constant, K_a
- Binding also depends on the molar concentrations of both drug and protein.
- For a single binding site on the protein, the association is simply summarized by the following reaction:

$$Drug + Protein \leftrightarrow Drug_Protein\ complex$$

■ ■ ■

$$K_a = \frac{C_b}{C_u \times P}$$

Where C_b- concentration of bound drug, C_u- concentration of unbound drug, and P- concentration of unoccupied protein.

- The unoccupied protein concentration (P) depends on the total protein concentration, P_t.

- These two concentrations are related by:

$$f_{u.P} = \frac{P}{P_t}$$

Where $f_{u.p}$ is the fraction of the total #sites unoccupied

■■■

- f_u can, then be expressed by:

$$f_u = \frac{1}{1 + K_a . f_{u.P} . P_t}$$

■ ■ ■

- A large variety of drugs ranging from weak acids, neutral compounds, and weak bases bind to plasma proteins.

- Acidic drugs generally bind to plasma **albumin** and basic drugs to α_1**-acid glycoproteins**;

- Binding to other plasma proteins (e.g., lipoproteins and globulins) occurs to a much smaller extent.

■ ■ ■

- For the majority of drugs, binding to plasma **albumin**, which comprises **>50%** of the total proteins, is quantitatively more important.

- The albumin can bind several compounds having varied structures, some substances even to a single site.

    - Groups of drugs that bind to the same site compete with each other for binding.

■ ■ ■

- Drug binding to tissue Proteins:
  - Many drugs accumulate in tissues at higher concentrations than those in the extracellular fluids and blood called **localization**.
  - Tissue binding of drugs generally is reversible; or some case irreversible (covalent chemical bonding).

■ ■ ■

- Tissue protein binding is important in distribution from two viewpoints:

    1. It increases the apparent volume of distribution (in contrast to plasma protein binding which decreases it)

    2. It results in localization of a drug at a specific site in the body producing local toxicity. Examples:

        - Gentamicin cause Nephro and vestibular toxicity.
        - Tetracyclines accumulate in bones and teeth
        - Paracetamol and chloroform metabolites cause hepatotoxicity

■ ■ ■

- Fat may serve as a reservoir for lipid-soluble drugs.
  - E.g. The highly lipid-soluble barbiturate, thiopental
  - Many lipid-soluble drugs are stored by physical solution in the neutral fat.
  - In obese persons, the fat content of the body may be as high as 50%, and even in lean individuals it constitutes 10% of body weight.

■ ■ ■

- Drug displacement interactions:
  - Drug displacement interactions occur between two or more drugs that bind to same plasma protein site.
  - If one drug is binding to such a site, then administration of second drug having higher affinity for the same site results in displacement of first drug from its binding site.
  - Generally, in many cases, the impact of interactions is minimal.

■ ■ ■

- In some instances a slight displacement of a drug will result in marked increase in its biological activity.
    - E.g. Administration of **phenylbutazone** to a patient on **warfarin** therapy results in displacement of warfarin from its binding site.

Protein binding determination

- **Spectral changes**
  - Most drugs have distinct UV spectra because of the conjugated chromophores in the molecule.
  - When a drug interacts with a protein the UV or visible spectrum may be changed because of alterations in the electronic configuration.
  - These alterations can be quantitated and used to determine the extent of binding.

■ ■ ■

- **Gel filtration**
  - This involves the use of porous gels that are molecular sieves.
  - These separate components on the basis of size.
  - Low molecular weight drugs are held on the gel whereas bound drug and protein are washed through.

■ ■ ■

- **Equilibrium dialysis**
  - The protein solution (e.g. plasma) containing drug and a buffer solution are placed on opposite sides of a dialysis membrane.
  - After a sufficient time (maybe 12- 24 hours), free drug concentration will be the same on either side of the membrane.
  - Protein binding can be determined by measuring the concentration of drug on either side of the membrane.
  - On left the concentration will involve free and bound drug, whereas on the right there is no binding and the concentration will equal to the free drug concentration.

■ ■ ■

- **Ultrafiltration**
  - A quicker method of separating free and bound drug is the ultrafiltration method.
  - Drug and protein solution are placed in a filter membrane and liquid containing free drug is forced through the membrane by centrifugation.

- Reading assignment:
  1. Drug distribution and Specialized Barriers
     - Blood Brain Barrier and Blood CSF Barrier
     - Placental Barrier
     - Other Barriers
  2. Drug distribution and Disease states
  3. Distribution and partition coefficients
  4. Redistribution??

■ ■ ■

- Assignment for presentation in a group of …?:
  - Individualization and optimization of drug therapy:
    1. Dosage regimen adjustment in renal impairment
    2. Dosage regimen adjustment in hepatic impairment
    3. Dosage regimen adjustment in Pediatrics
    4. Dosage regimen adjustment in Geriatrics
    5. Dosage regimen adjustment in Obesity
    6. Pharmacokinetic drug interactions in combination therapy

Drug Elimination

- Elimination is the **irreversible** loss of drug from the site of measurement.
- Two processes:
  - **Excretion**: the irreversible loss of chemically unchanged drug
  - **Metabolism**: the conversion of one chemical species to another.

■ ■ ■

- Biotransformation of drugs - chemical alteration of the drug in the body.
    - Aim: to convert non-polar lipid soluble compounds to polar lipid insoluble compounds which are readily excretable.
    - Most hydrophilic drugs are less bio-transformed and excreted unchanged (e.g. streptomycin).

■ ■ ■

- Two phases of biotransformation:
- **Phase I** or Non-synthetic
  - Metabolite may be active or inactive
  - Metabolites are too lipophilic to be retained in the kidney tubules
  - Oxidation, Reduction and Hydrolysis reactions

■ ■ ■

- **Phase II** or Synthetic
  - Results in polar, usually more water-soluble compounds that are most often therapeutically inactive
  - Such as glucuronic acid, sulfuric acid, acetic acid, or an amino acid
  - Conjugation reactions

■ ■ ■

- First-order kinetics (metabolism):
  - The rate of drug metabolism is directly proportional to the concentration of free drug, i.e., a constant fraction of drug is metabolized per unit of time.
- Zero-order kinetics (metabolism):
  - As the amount of drug rises in the plasma, certain processes that have limited capacity become saturated (limited amount of enzymes even if dose increases).
  - Example: Aspirin, Ethanol, and Phenytoin

...

- Several of the transformations (metabolism) takes place in the endoplasmic reticulum of the liver and of certain other tissues.

- Endoplasmic vesicles called **microsomes** are important

  - Metabolizing enzymes of the endoplasmic reticulum are called **microsomal enzymes**.

  - Drug metabolism, therefore, may be classified as microsomal and non-microsomal.

■ ■ ■

- The major enzymes responsible for the oxidation and reduction of drugs belong to the superfamily of **cytochrome P450** enzymes.

- The isozymes of this family display a relatively high degree of structural specificity; a drug is often a good substrate for one enzyme but not another.

Clearance (CL)

- The clearance of a drug is the theoretical volume of plasma from which drug is completely removed in unit time.
- Of the concepts in PK, clearance has the greatest potential for clinical applications.
- It is also the most useful parameter for the evaluation of an elimination mechanism.

■ ■ ■

- For a linear PK, rate of elimination is proportional to the plasma concentration of the drug.
  - Clearance is defined as the **proportionality** factor relating rate of drug elimination to the plasma concentration.

$$Rate\ of\ Elimiation = CL \times C_p$$

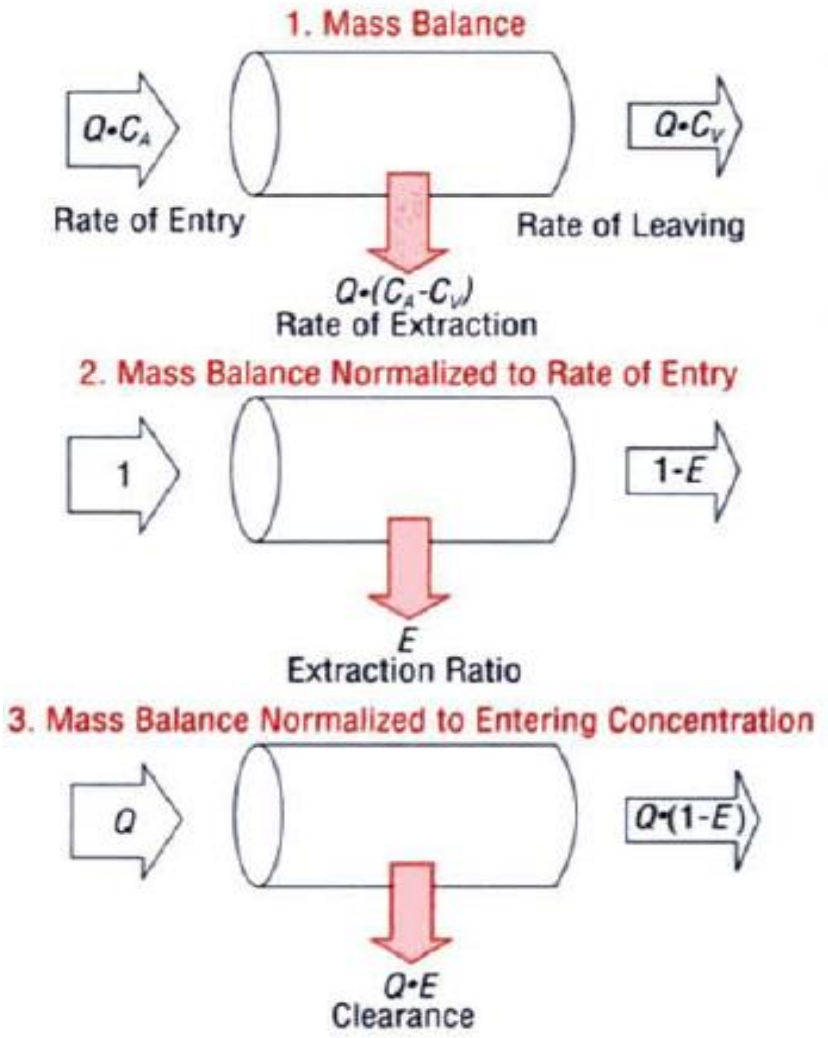


Fig. The extraction of a drug by an eliminating organ under steady state condition from the fundamental concepts of mass balance.

■■■

- Clearance can be described in terms of the eliminating organ.
    - E.g., hepatic clearance, renal clearance, or pulmonary clearance.
- It can also be described as renal clearance and extra renal clearance.
- It is also described by the nature of the elimination process as metabolic clearance or excretory clearance.

■ ■ ■

- Furthermore, the clearance value depends on the reference fluid.
  - **Hepatic** metabolic plasma **clearance**
  - **Renal** excretory plasma **clearance**
- In practice the term plasma is dropped, as plasma is the common site of measurement.

■ ■ ■

- For many applications in PK, it matters little whether clearance measurements are based on drug in plasma or in blood.
  - The exception is when a clearance value is used to estimate extraction ratio.
  - Then, the blood clearance value must be used, because it is this parameter that directly relates to organ flow and extraction ratio.

■ ■ ■

- Plasma clearance is more frequently reported than blood clearance.

- Thus, if one wishes to estimate extraction ratio, one needs to convert this clearance value based on drug concentration in plasma to one based on the concentration in blood.

- This conversion is accomplished by experimentally determining the blood-to-plasma concentration ratio.

■ ■ ■

- Since, the products of the respective clearance and concentration terms, based on measurements in blood and plasma, are equal to the rate of elimination, it follows that:

$$\frac{Plasma\ clearance}{Blood\ clearance} = \frac{Blood\ concentration\ (C_b)}{Plasma\ concentration\ (C_p)}$$

...

- The anatomy of the human dictates that the clearance of a drug by one organ **adds** to clearance of another.

- Consider, for example, a drug that is eliminated by renal excretion and hepatic metabolism. Then:

$$\text{Rate of elimination} = \text{Rate of renal excretion} + \text{Rate of hepatic metabolism}$$

...

- Dividing the rate of removal associated with each process by the incoming drug concentration (blood or plasma), which for both organs is the same gives the clearance:

$$\frac{\text{Rate of elimination}}{C} = \frac{\text{Rate of renal excretion}}{C} + \frac{\text{Rate of hepatic metabolism}}{C}$$

$$\text{Total clearance} = \text{Renal clearance} + \text{Hepatic clearance}$$

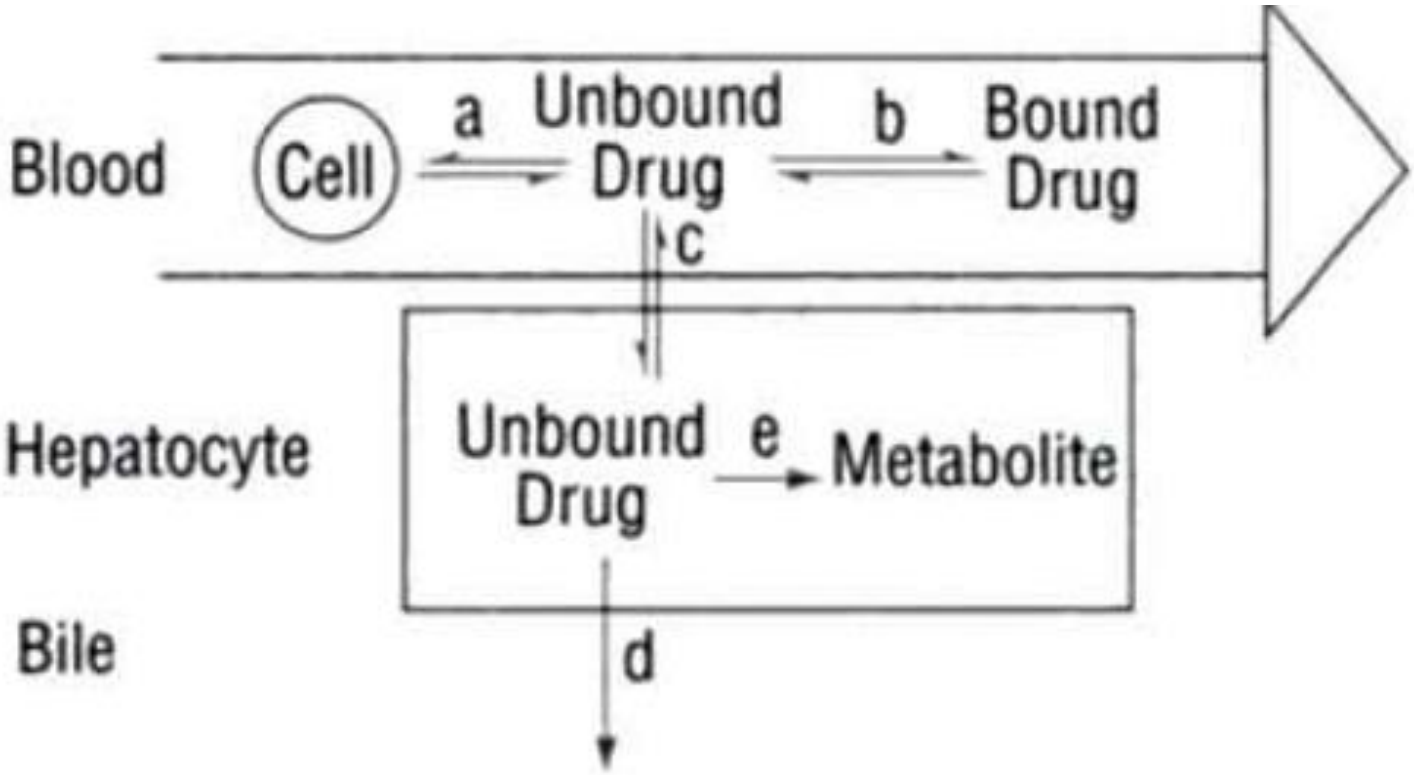
Hepatic Clearance

- The most direct quantitative measure of the liver's ability to eliminate a drug is **hepatic clearance**.

- Hepatic clearance includes biliary excretory clearance and hepatic metabolic clearance.

$$Hepatic\ blood\ clearance\ (CL_{b,H}) = Q_H \times E_H$$

Where, Q_H-Hepatic blood flow, and E_H-Hepatic extraction ratio


Blood
Cell
a
Unbound Drug
b
Bound Drug
c
Hepatocyte
Unbound Drug
e
Metabolite
Bile
d

■ ■ ■

- Changes in clearance and extraction ratio are associated to alterations in **perfusion**, **PPB**, or **inherent elimination characteristics**.

  - When clearance is perfusion rate-limited, there is so much hepatocellular activity; so that almost all the drug presented is extracted.

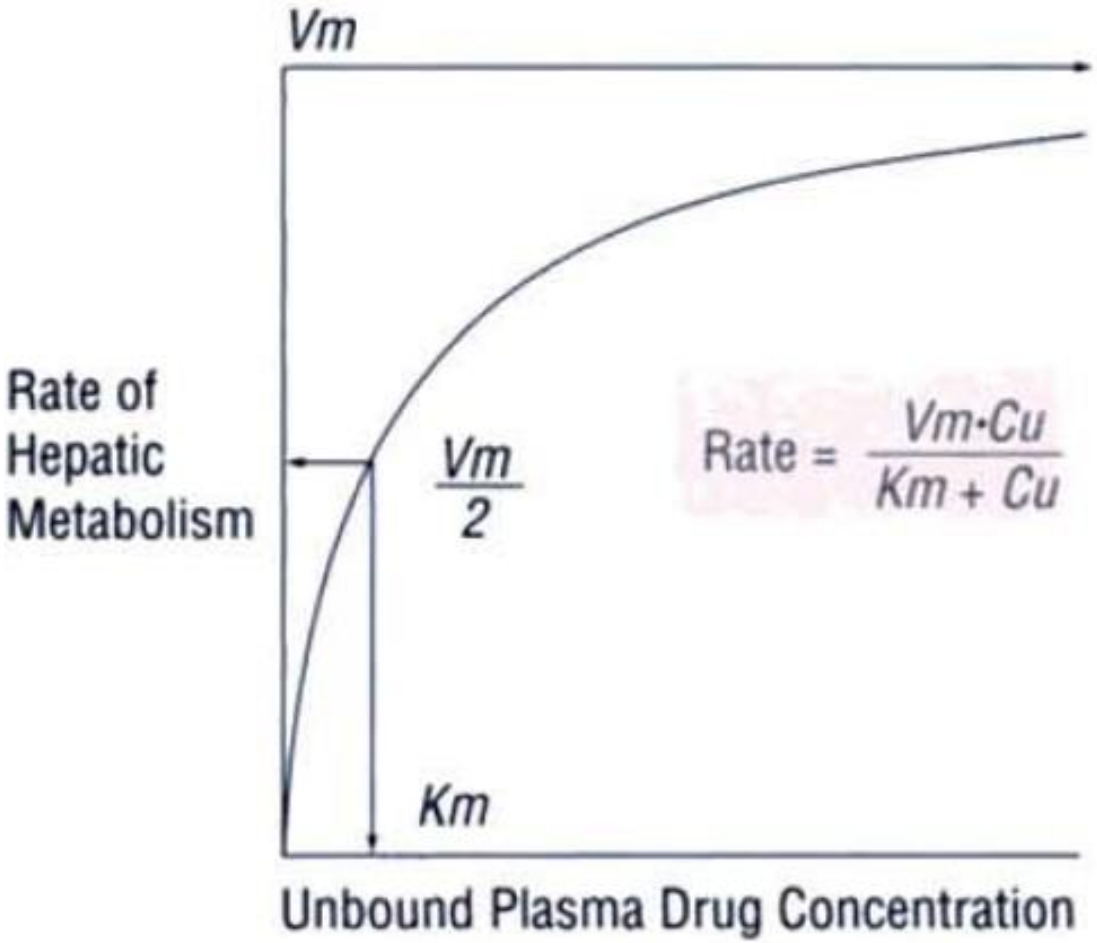
  - Conversely, if enzyme activity is the rate-limiting step, then clearance is low and directly proportional to activity (E.g., when changed by induction or inhibition by another drug).

■ ■ ■

- The basic principles of **enzyme kinetics** have application in PK.
  - These systems are relatively specific with respect to substrate and have finite capacities.
  - Frequently, the kinetics of these capacity-limited processes can be described by the **Michaelis-Menten equation**:

$$Rate\ of\ Metabolism = -\frac{dC}{dt} = \frac{V_m \times C}{K_m + C}$$

Where, K_m- Michaelis-Menten constant


Vm
Rate of Hepatic Metabolism
Vm / 2
Rate = Vm·Cu / Km + Cu
Km
Unbound Plasma Drug Concentration

■ ■ ■

- In enzyme kinetics, the value of **Vm** is directly proportional to the **total concentration of enzyme**,
- Km is an inverse function of the affinity between drug and enzyme.
- Unbound metabolic clearance is defined as the rate of metabolism relative to the unbound plasma concentration:

$$Unbound\ metabolic\ clearance = \frac{V_m}{K_m + C_u}$$

■ ■ ■

- Note that the highest clearance is the ratio Vm/Km, a value often called the **intrinsic metabolic clearance**.
    - The value may be so high that elimination *in vivo* is perfusion rate-limited.

■ ■ ■

- **Models of hepatic elimination** have been developed to quantify changes in clearance when perfusion, plasma protein binding, and enzyme activity are altered.

- The **well-stirred model** is one of these models.

    - This model allows one to predict those situations in which either **clearance** or **extraction ratio** is affected and the expected direction of change.

■ ■ ■

- Well-stirred model states that:

$$CL_{b,H} = \frac{Q_H \times fu_b \times CL_{int}}{Q_H + fu_b \times CL_{int}}$$

Where, Q_H- is the hepatic blood flow; CL_{int}- is the intrinsic clearance that relates rate of metabolism to unbound concentration at the enzyme site, and fu_b- is the fraction unbound in blood.

- The hepatic extraction ratio, $CL_{b,H}/Q_H$, is then:

$$E_H = \frac{fu_b \times CL_{int}}{Q_H + fu_b \times CL_{int}}$$

■ ■ ■

- When E_H approaches 1.0 (the perfusion rate-limited condition), $fu_b \times CL_{int}$ is much greater than Q_H, and clearance approaches Q_H.
    - Changes in CL_{int} and f_u here are not expected to influence CL_H and E_H much.
- Conversely, when E_H is small, Q_H must be much greater than CL_{int}.
    - E_H and $CL_{b,H}$ are approximated by $\frac{fu_b \times CL_{int}}{Q_H}$ and $fu_b \times CL_{int}$ respectively: the value of the extraction ratio depends on all three factors, whereas clearance depends only on fu_b and CL_{int}.

■ ■ ■

- Read
  - Bioavailability and first pass consideration.
  - Biliary excretion and Enterohepatic cycling.

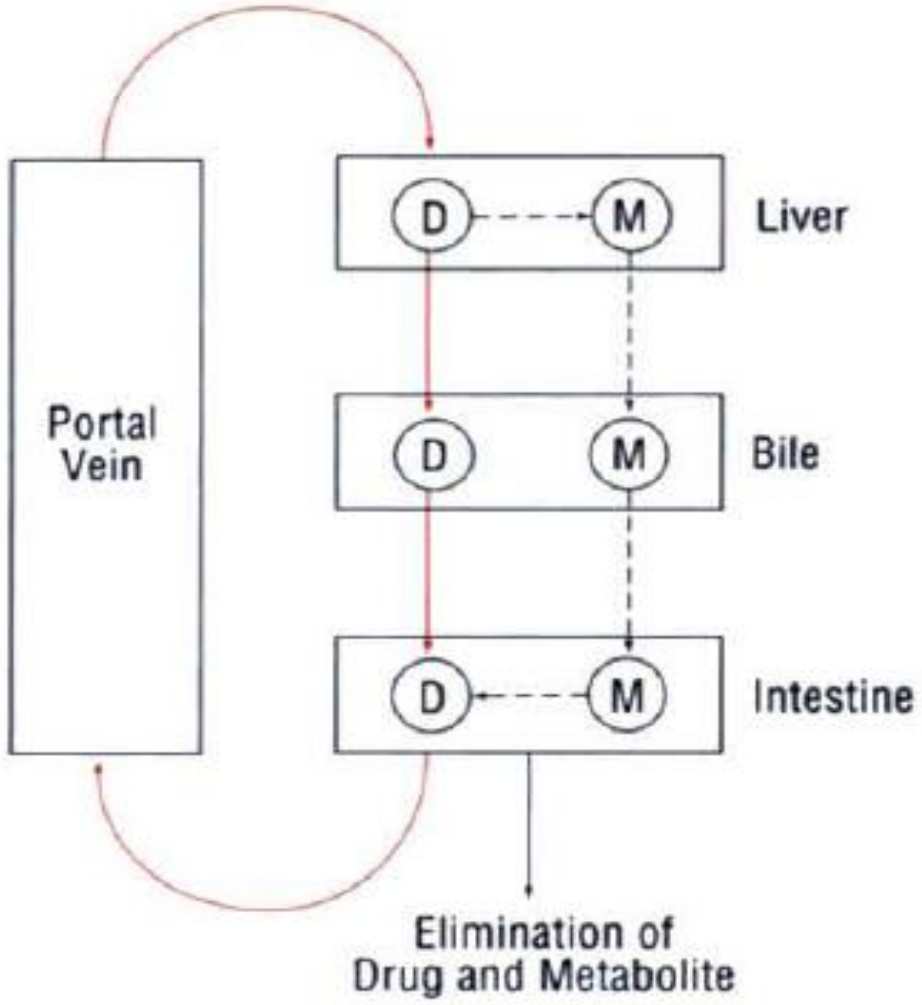


Fig. Enterohepatic cycling of the drug (D) or its metabolite (M).

Renal Clearance

- When the rate of urinary excretion is directly proportional to the plasma drug concentration,

$$Rate\ of\ excretion = CL_R \times C$$

  - Renal clearance is a constant.
  - This constancy forms the basis for the use of urine data to determine the time course of a drug in the body.

■ ■ ■

- Appearance of drug in the urine is the **net result** of filtration, secretion, and reabsorption.

- The excretion rate is, therefore,

$$Rate\ of\ excretion = (1 - F_R)[Rate\ of\ Filtration + Rate\ of\ Secretion]$$

Where, F_R-is fraction reabsorbed from the lumen

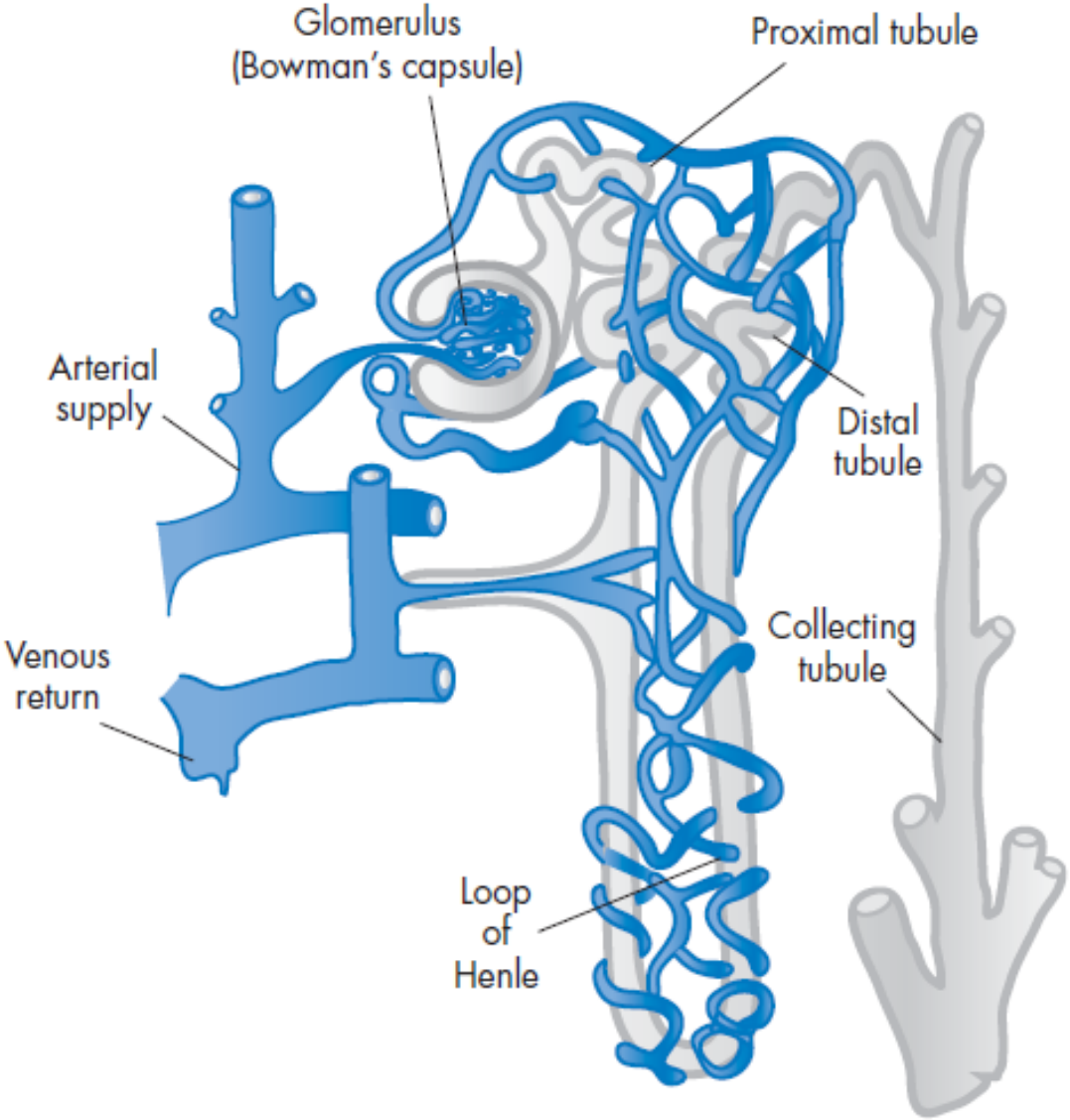


Fig. The functional nephron.

■■■

- The rate at which plasma water is filtered, 120 ml/min in a 70-kg 20-year-old man, is conventionally called the glomerular filtration rate, **GFR**.

- It follows that:

$$Rate\ of\ filtration = GFR \times C_u$$

- Recall that f_u is the ratio of the unbound drug concentration to total plasma drug concentration; therefore,

$$Rate\ of\ filtration = f_u \times GFR \times C_P$$

■ ■ ■

- If a drug is only filtered and all filtered drug is excreted, then the rate of excretion is the rate of filtration.

- Since renal clearance, CL_R, by definition is:

$$CL_R = \frac{Rate\ of\ excretion}{Plasma\ concentration}$$

- It follows that for such a drug its CL_R (by filtration) is $f_u \times GFR$.

...

- Read
  - Extra-renal excretion